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ORIGINAL ARTICLE

Contemporary management and classification of hepatic leiomyosarcoma

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Abstract

Background: Hepatic leiomyosarcomas are rare soft-tissue tumours. The majority of lesions previously considered as leiomyosarcomas have been identified as gastrointestinal stromal tumours (GISTs). Consequently, understanding of the role of liver resection for true leiomyosarcoma is limited, a fact that is exacerbated by the increasing recognition of leiomyosarcoma subtypes. This study presents data on the outcomes of liver resection for leiomyosarcoma and suggests an algorithm for its pathological assessment and treatment.

Methods: Patients were identified from a prospectively collected departmental database. All tumours were negative for c-kit expression. Immunohistochemistry was performed to identify the presence of oestrogen or progesterone receptor (OR/PR) expression or Epstein–Barr virus (EBV) and patients were stratified according to this profile.

Results: Eight patients (of whom seven were female) underwent a total of 11 liver resections over a 12-year period. One patient had a primary hepatic leiomyosarcoma. Of those with metastatic leiomyosarcomas, the primary tumours were located in the mesentery, gynaecological organs and retroperitoneum in four, two and one patient, respectively. Both leiomyosarcomas of gynaecological origin stained positive for OR/PR expression. One patient had previously undergone renal transplantation; this leiomyosarcoma was associated with EBV expression. Median survival was 56 months (range: 22–132 months) and eight, six and four patients remained alive at 1, 3 and 5 years, respectively.

Conclusions: Hepatic resection for leiomyosarcoma is associated with encouraging rates of 5-year overall and disease-free survival. The worse outcome that had been expected based on data derived from historical cohorts (partly comprising subjects with GIST) was not observed. An algorithm for pathological classification and treatment is suggested.

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Introduction

For common liver tumours, such as colorectal liver metastases (CLM), longterm outcomes in large patient cohorts have been comprehensively reported.[1] Experiences of treating patients with non-colorectal, non-neuroendocrine tumours are, however, much less common. Understanding the role of surgical intervention in primary or metastatic hepatic leiomyosarcoma is complicated by the low prevalence of the disease and the evolution of the pathological understanding of smooth muscle tumours (SMTs), of which leiomyosarcoma is one type.[2]

Several case series have described the outcomes of patients undergoing resection of hepatic leiomyosarcoma.[3–7] Although survival does not mirror the experience of patients treated for CLM, an increase in survival over non-operated patients is observed and cure is possible. The identification of gastrointestinal stromal tumours (GISTs) as a distinct subtype of SMT, however, requires the careful reinterpretation of previously reported series. The

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histological features of GIST and leiomyosarcoma are similar and the two entities are separated by analysis for c-kit proto-oncogene expression. The less aggressive growth pattern of GIST and its potential for treatment with tyrosine kinase inhibitors renders this a clinically important distinction. A review of previously published series of patients submitted to resection of hepatic leiomyosarcoma has attempted to estimate the respective proportions of GISTs and true hepatic leiomyosarcomas.[7] A further series described outcomes in patients with hepatic GIST and leiomyosarcoma.[3] However, this series recruited patients prior to the identification of c-kit expression and did not explain its method of identifying patients with GIST or leiomyosarcoma.[8]

Evolution in the pathological description of abdominal leiomyosarcoma has led to the recognition of subtypes related to Epstein–Barr virus (EBV) infection and oestrogen and/or progesterone receptor (OR/PR) expression. The purposes of this study are to report the outcomes of liver resection amongst patients with true leiomyosarcoma, to review the histology of these cases and to suggest an approach to the identification and treatment of the different forms of leiomyosarcoma.

Materials and methods

Adult patients submitted to resection of hepatic leiomyosarcoma at a single institution between 1999 and 2010 were retrospectively identified from a prospectively maintained database. Patient demographic details, investigations, treatments, complications, pathological variables, and outcomes (survival and disease-free status) were identified.

Pathological specimens were re-evaluated for this study by a pathologist with a specialist interest in SMTs (WM). Cases were included if they were negative for CD 117 (c-kit) expression and positive for smooth muscle actin and desmin, thereby confirming leiomyosarcoma as the tumour type. The Trojani system was used to grade the samples. To further sub-classify tumours, immunohistochemistry (IHC) was performed to assess OR/PR expression and quantitative polymerase chain reaction (PCR) analysis was conducted to identify EBV within archived tissue. Positive and negative controls were included.

Results

Group demographic details and primary disease

Over 12 years, 11 of a series of 2397 hepatic resections (0.46%) were performed for leiomyosarcoma. These procedures were conducted in eight patients (range per patient: 1–3 resections). The median age at initial presentation was 58 years (range: 40–71 years). Seven of the patients were women. Primary leiomyosarcoma originated from the bowel or mesentery ($n = 4$), gynaecological organs ($n = 2$) or retroperitoneum ($n = 1$); there was a single case of primary hepatic leiomyosarcoma. The median interval between primary leiomyosarcoma and identification of metastatic hepatic leiomyosarcoma was 29 months (range: 6–58 months). Table 1 provides a summary of each patient's history.

Hepatic disease

The median number of segments resected was two (range: 1–7 segments). Complications affected three patients; two required a second operation to control haemorrhage, and one suffered temporary liver dysfunction with cholestasis and ascites. The median length of hospital stay was 11 days (range: 7–28 days). There were no postoperative deaths (within 90 days).

Survival

At 1, 3 and 5 years, eight, six and four patients, respectively, remained alive. Seven, five and three patients, respectively, remained disease-free at these time-points. All deaths were caused by disease prior to these time-points. Of the four patients alive at 5 years, two subsequently died (one of disease) and two remained alive (one with disease). The median survival was 56 months (range: 22–132 months) and the median disease-free survival was 46.5 months (range: 11–132 months). Six resections were associated with an R0 resection margin, in one of which local recurrence occurred. Five resections were associated with an R1 resection margin and four of these were affected by local recurrence.

Histological assessment

All tumours demonstrated characteristic features (Figs 1 and 2) and positivity for smooth muscle actin and desmin (Fig. 3). Seven were metastatic leiomyosarcomas of Trojani grade 1 ($n = 2$), grade 2 ($n = 2$) and grade 3 ($n = 3$). Two tumours were positive for OR expression (Fig. 4). The solitary primary hepatic leiomyosarcoma displayed features of a low-grade tumour with much less cellular atypia than metastatic leiomyosarcoma and was positive for EBV expression as assessed by PCR (Fig. 5). This patient had undergone previous renal transplantation and was receiving immunosuppressive therapy.

Discussion

This study aimed to present the outcomes of patients undergoing surgical treatment for primary and metastatic hepatic leiomyosarcomas in light of the identification of distinct subtypes of leiomyosarcoma and is the first to do so. This follows the realization that GIST is a distinct pathological type of SMT that can be distinguished from leiomyosarcoma, typically, by expression of the proto-oncogene c-kit, CD117.[8] Patients with metastatic GIST have more favourable outcomes than those with leiomyosarcoma as a result of the medical therapies available.[6,9] Consequently, previous studies describing outcomes following resection of hepatic 'leiomyosarcoma' may be unreliable because they included unknown or estimated numbers of patients with GIST.[3–7] Despite the aggressive nature of leiomyosarcoma, patients in the present cohort demonstrated encouraging survival outcomes not dissimilar to those demonstrated by patients with resected CLM. The study is weakened by its small patient cohort, although this may reflect careful patient selection. However, several patients

Table 1 Summary of the presented cases

Age at first liver operation and sex	Primary site and treatment	Interval between primary and metastatic disease, months	Description of hepatic metastases and resection (date)	Postoperative complications (length of postoperative stay)	Trojani grade of first liver tumour	Liver resection status	Duration of survival following first liver resection and disease status
60 F	Retroperitoneum Local resection	45	Segments IV–VII Right hepatic trisectionectomy, distal pancreatectomy, splenectomy, resection of pelvic mass (July 1999)	Postoperative haemorrhage, laparotomy (13 days)	1	R1	53 months Died of recurrent disease Extrahepatic metastasis
56 F	Vulva Wide local excision	58	Segments V, VI Right hepatectomy (May 2001)	Nil (7 days)	2	R0	110 months Died of recurrent disease Extrahepatic metastasis
40 F	Primary hepatic leiomyosarcoma	NA	Segment I Non-anatomical resection (October 2002) Segments V, VI and right kidney Non-anatomical resection and right nephrectomy (July 2011)	Nil (14 days) Nil (14 days)	1	R0 R0	Died after 132 months Disease-free
60 F	Jejunum Small bowel resection	31	Segment IV Left hepatectomy including middle hepatic vein (September 2003)	Nil (11 days)	3	R1	22 months Recurrent disease Lost from follow-up and presumed dead
62 F	Greater omentum Local resection	6	Segments III, IVb Non-anatomical resection (February 2008)	Nil (3 days)	3	R0	71 months, alive Disease-free
49 F	Small bowel mesentery Small bowel resection	29	Segments V, VI and mass in tail of pancreas Distal pancreatectomy segments V, VI metastasectomy (January 2009) Recurrent disease segments II–VIII Redo resection – right hepatic trisectionectomy and segments II, III metastasectomies (December 2009) Redo-redo liver resection – non-anatomical resection (March 2011)	Postoperative haemorrhage, laparotomy (7 days) Nil (9 days) Nil (7 days)	1	R1 R1 R1	59 months, alive Recurrent hepatic disease
46 M	Rectal mesentery En bloc resection with rectum	16	Segments I–VI and VIII Single stage right trisectionectomy and segments I–III metastasectomies (May 2010)	Temporary ascites (19 days)	3	R0	26 months Died of recurrent pulmonary metastases
71 F	Cervix Hysterectomy and oophorectomy	18	Segments IV, V, VIII Non-anatomical resection (August 2010)	Respiratory failure (CPAP) (28 days)	2	R0	40 months alive Disease-free

F, female; M, male; CPAP, continuous positive airway pressure.

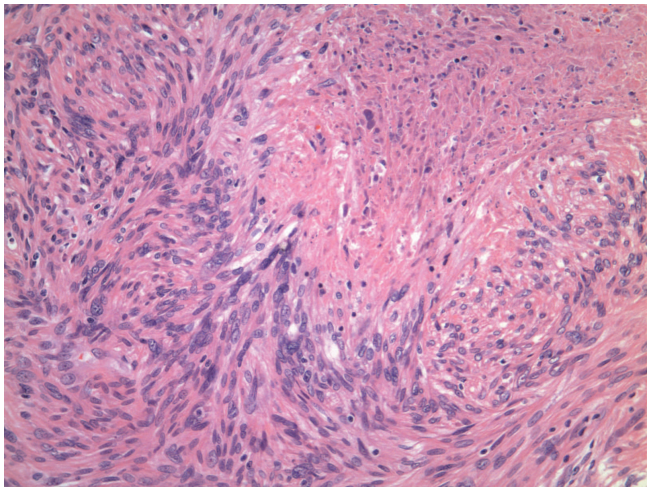

Figure 1 Histopathology of a section of a leiomyosarcoma (not otherwise specified) demonstrates spindle cell malignancy with zones of necrosis typical of this tumour. (Haematoxylin and eosin stain; original magnification ×200)

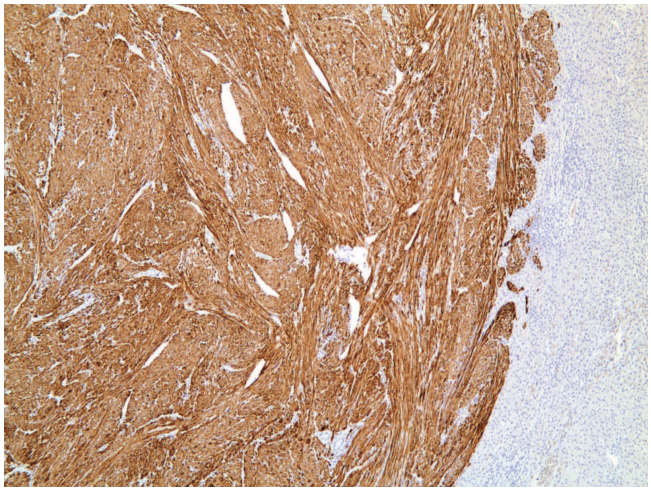

Figure 3 Immunohistochemistry for desmin shows strong cytoplasmic positivity typically seen in smooth muscle. (Original magnification ×50)

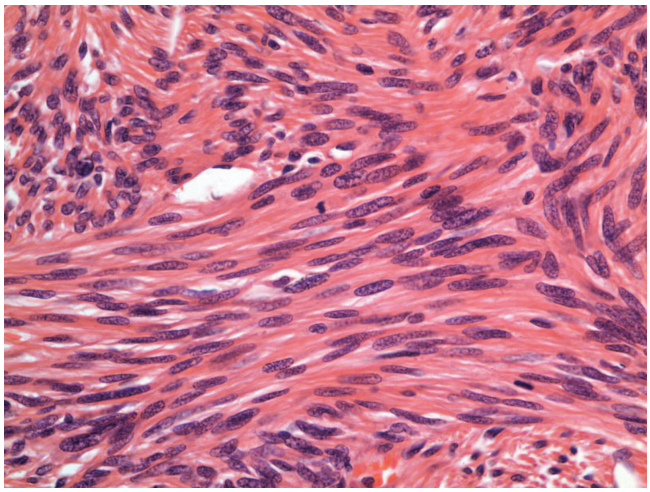

Figure 2 Histopathology at higher magnification of a leiomyosarcoma (not otherwise specified) demonstrates mitosis, interlacing fascicles, pink cytoplasm and central cigar-shaped nuclei. (H&E stain; ×400)

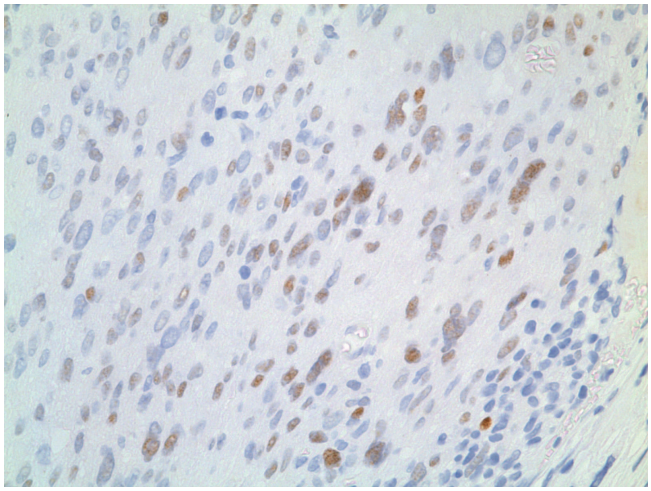

Figure 4 Immunohistochemistry in a leiomyosarcoma of gynaecological origin shows positivity for nuclear oestrogen receptor expression (Original magnification ×400)

underwent extensive hepatic resection or multivisceral resection, which suggests the patient cohort was not comprised of patients with favourable outcomes prior to initial liver resection. Obtaining an R0 resection margin appears to relate to disease-free survival and should be achieved when possible. An R1 resection margin does not exclude disease-free survival, but should stimulate intensive radiological follow-up as repeat resection is feasible.

The Trojani histological grade was assessed in all cases. This did not seem to impact on survival, which indicates that even patients with high-grade tumoursmay benefit from surgical resection. The description of three distinct subtypes of hepatic leiomyosarcoma has clinical relevance. Assessment for OR nuclear expression and EBV status should be performed to stratify cases. In the present series, leiomyosarcoma of the conventional type was the most prevalent form.

The expression of OR was identified in two patients; the majority of primary tumours arise in the smooth muscle of the gynaecological tract, which is sensitive to oestrogen, and have OR expression. Most benign tumours are positive for OR, but with malignant progression this can be lost.Medical therapy targeted at the hormone receptor status of these tumours is of unclear clinical

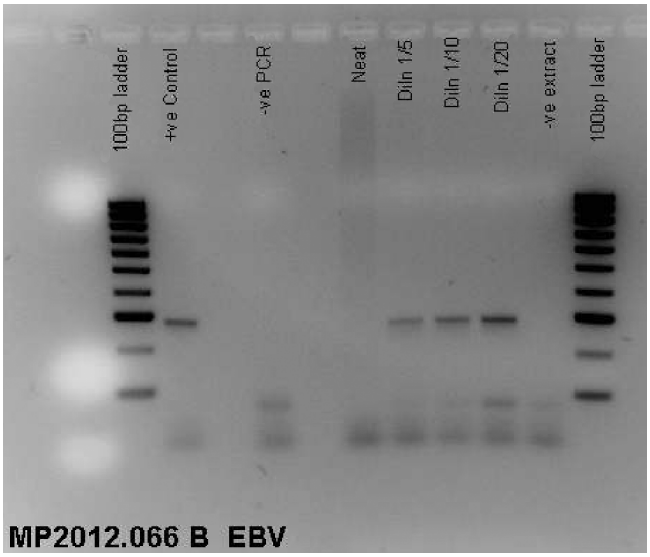

Figure 5 Polymerase chain reaction analysis (PCR) is positive for Epstein–Barr virus (EBV). *EBV is detected (dilution 1/5, 1/10 and 1/20) in patient 8 as confirmed by the positive and negative controls. The positive control is indicated by the arrow

benefit. The use of aromatase inhibitors in advanced uterine leiomyosarcoma has shown promise in small case series,[10,11] but a partial response to treatment was observed in only three of a larger cohort of 24 patients.[12] In another study, a response was observed in just one of 28 patients with uterine leiomyosarcoma treated with tamoxifen.[13]

The single case of EBV leiomyosarcoma in this series illustrates typical features of this disease; it is a rare tumour[14] characterized by its development following a period of immunosuppression. This occurs in two settings in, respectively, patients with human immunodeficiency virus (HIV) infection[15–17] and in those with immunosuppression following solid organ transplantation.[18–23] Immunosuppression appears to be the key regulator of leiomyosarcoma EBV disease progression. Rapid growth of hepatic leiomyosarcoma EBV was observed following liver transplantation in a 2-year-old child.[18] Immunosuppression was subsequently reduced and then withdrawn in line with the lack of progression of leiomyosarcoma. At 12 years following transplantation, the patient was found to be symptom-free. Thus the reduction or withdrawal of immunosuppression should be considered when possible. Figure 6 proposes a classification and treatment algorithm for SMTs.

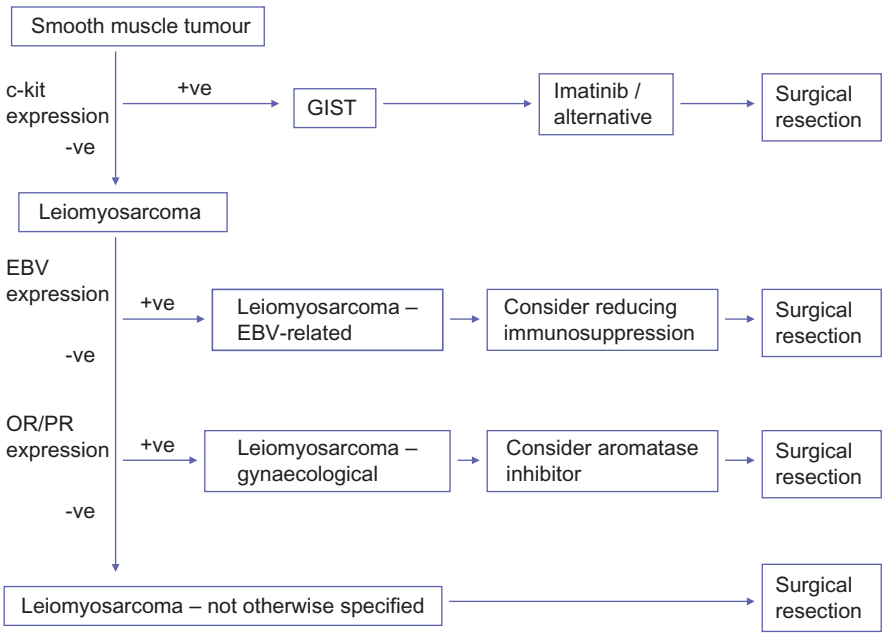

Figure 6 Proposed algorithm for the pathological classification and management of abdominal smooth muscle tumours (SMTs) based upon histological assessment. Immunohistochemistry permits the stratification of SMTs into subgroups with implications for the patient's clinical management whereby gastrointestinal stromal tumours (GISTs) and gynaecological leiomyosarcomas may be treated with medical therapy, and Epstein–Barr virus (EBV)-related leiomyosarcoma by modifying immunosuppression. Primary and metastatic disease should be treated by surgical resection where possible. OR/PR, oestrogen/progesterone receptor

Conclusions

Hepatic resection of leiomyosarcoma is associated with encouraging rates of 5-year overall and disease-free survival. The worse outcome predicted on the basis of findings in historical cohorts (partly comprising subjects with GIST) was not observed. Immunohistochemistry characterizes subgroups of leiomyosarcoma as of gynaecological origin, EBV-related and as not otherwise specified. The potential roles of hormonal therapy and the modulation of immunosuppression in the first two subtypes are yet to be fully explored. Although hepatic leiomyosarcoma is a rare entity, the proposed algorithm provides a contemporary classification and strategy for the management of hepatic leiomyosarcoma.

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Conflicts of interest

None declared.

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